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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,301	10/24/2003	Gary K. Schwartz	702-A-US	1477

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EXAMINER	
MARTIN, PAUL C	
ART UNIT	PAPER NUMBER
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,301	SCHWARTZ, GARY K.	
	Examiner	Art Unit	
	Paul C. Martin	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-38 and 41-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *34-35,38,46 and 47* is/are allowed.

6)☒ Claim(s) *31-33,36,37,41-45 and 48-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 31-38 and 41-50 are pending in this Application and were examined on their merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

The drawings were received on 11/27/06. These drawings are accepted.

Response to Amendment

The Declaration under 37 CFR 1.132 filed 11/27/06 is insufficient to overcome the rejection of claims 31-38, 41 and 42 based upon Li *et al.* as set forth in the last Office action because: The Applicant's opinion and assertion that the lack of *in vivo* data would not lead to a reasonable expectation of success in adapting the method of Li *et al.* to treat cancer in a subject is without basis.

The MPEP states:

Similarly, courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. The Federal Circuit, in Cross v. Iizuka, 753 F.2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985), commented on the significance of data from in vitro testing that showed pharmacological activity: We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility. The Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States. FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Scott [v. Finney], 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 [(Fed.Cir. 1994)]. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Claim Rejections - 35 USC § 112

The rejection of Claims 36-38 and 42 under 35 U.S.C. § 112, 2nd paragraph as being indefinite has been withdrawn due to the Applicant's amendments to the Claims filed 11/27/06.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41, 42 and 48 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method wherein the therapeutic microtubule-destabilizing agent is the taxol-like nocodazole, does not reasonably provide enablement for a method wherein the therapeutic microtubule-destabilizing agent is any taxol compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There is no guidance or direction presented to direct one to determine which substances would work in the broadly claimed invention, which is a complex and unpredictable art. Therefore because of the large number of inoperable embodiments claimed, the ordinary artisan would be subjected to undue experimentation to practice the claimed invention.

The enablement is not commensurate in scope with claims drawn to a method wherein the therapeutic microtubule-destabilizing agent is any taxol compound.

The entire scope of the claims has not been enabled because:

1. Quantity of experimentation necessary would be undue because of the large proportion of inoperative compounds claimed.

The Applicant's disclosure only teaches the effective use of one example of taxol-like microtubule destabilizing agent, whereas Lin *et al.* teaches that the taxol Paclitaxel mitigates the berberine-induced growth inhibition of tumor cells (Pg. 419, Fig. 3) and that whether berberine has synergistic or antagonistic effects with other chemotherapeutic drugs is not clear (Pg. 420, Column 2, Lines 1-6). Therefore, the Applicant's invention is not enabled for at least on taxol, and on of ordinary skill in the art would necessarily have to practice undue experimentation in testing and screening any other taxol compound for either synergistic or antagonistic effect.

2. Amount of direction or guidance presented is insufficient to predict which substances encompassed by the claims would work.

The Applicant's disclosure provides scant guidance or direction as to what other compounds are encompassed by the broad class of taxol compound, and provides only one specific example of such a compound which works in the instant invention.

3. Presence of working examples are only for specific substances and extension to other compounds has not been specifically taught or suggested.

As stated above, the instant disclosure only provides one working example of a specific microtubule-destabilizing agent, that of the taxol-like compound nocodazole. Applicant claims however, that the therapeutic agent encompasses a generic range of any taxol or taxol-like compounds.

4. The nature of the invention is complex and unpredictable.

As taught by Lin *et al.* above, at least one taxol exhibits an antagonistic effect when used with berberine, and the potential antagonistic or synergistic effects of berberine with other compounds remains undefined in the art.

In re Wands, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Also, due to the unpredictability of the chemical and biotechnological arts the extension of the substances provided in the working example of the specification to other taxols is highly uncertain. There is no direction to determine the optimum combination and selection of compounds, beyond experimentation to determine the effectiveness of each and every taxol or taxol-like compound.

The above claimed processes are not enabled because the Applicants were not in possession of the methods to perform their stated functions as claimed at the time the invention was made. Further, the specification does not include a teaching of how to make and use the claimed processes for their stated functions. There is only speculation and conjecture set forth in the specification regarding the processes but no specifics or other examples beyond the taxol-like nocodazole of how to perform the claimed processes (the method wherein the therapeutic microtubule-destabilizing agent

is any taxol compound)., i.e. it would require undue experimentation to determine precisely what the claimed methods would work for.

Claim Rejections - 35 USC § 103

Claims 31 and 32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (2000) for reasons of record set forth in the Action mailed 09/26/06.

The rejection of Claims 31-33, 34-38, 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (2000) in view of Lin *et al.* (1999) has been withdrawn because the Applicant's arguments with respect to the experimental results of Lin *et al.* were found to be persuasive. However, upon further consideration new grounds for rejection are made in view of Zhang *et al.* (1990).

Claims 31-33, 36, 37, 43, 44, 45, 49 and 50 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Li *et al.* (2000) in view of Zhang *et al.* (1990).

Li *et al.* teaches a method for inhibiting the cell growth in human (gastric, colon and breast) cancer cells by administering an effective amount or aqueous chinesis extract comprising the active ingredient berberine (Pg. 1287, Column 2, Lines 10-19 and Pg. 1288, Column 1, Lines 1-7 and Pg. 1289, Fig. 1). Li *et al.* teaches that

huanglian is part of a class of novel agents that inhibit tumor growth and suggests the use of huanglian as an oral anticancer drug (Pg. 1293, Column 1, Lines 45, 46 and 54-57).

Li *et al.* teaches that 100% tumor growth inhibition can only be achieved using the whole herbal extract, rather than its individual components, for cancer therapy (Pg. 1293, Column 1, Lines 25-34).

Li *et al.* does not teach wherein the cancer is a solid tumor, or the administration of an effective amount of aqueous *coptis chinesis* extract and a therapeutic agent, wherein the administration is performed in a sequential manner with *coptis chinesis* extract first then a therapeutic agent.

Zhang *et al.* teaches a method for treating solid tumors in rats comprising administering aqueous berberine, then the chemotheraprutic agent BCNU in a sequential manner (Pg. 660, Column 1, Lines 23-36 and Pg. 661, Fig. 5).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the method of Li *et al.* for inhibiting the cell growth in human cancer cells by administering an effective amount or aqueous chinesis extract

with the sequential administration of berberine and a therapeutic agent as taught by Zhang *et al.* because both methods are drawn to the use of berberine as a cancer treatment. One of ordinary skill in the art would have been motivated to combine the two methods because of the increased cancer treatment effectiveness of berberine and the therapeutic agent BCNU as taught by Zhang *et al.* above. There would have been a reasonable expectation of success in combining the two methods because both methods are drawn to the examination of the effects of coptis chinesis components on human cancer cells.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments filed 11/27/06 have been fully considered but they are not persuasive.

The Applicant argues that the *in vitro* data of Li *et al.* would not provide one of ordinary skill in the art a reasonable expectation of success in using aqueous chinesis

extract to treat cancer in a subject because whether a drug or composition will be useful in clinic can only be determined by vigorous clinical trials (Remarks, Pg. 12, Lines 5-16)

The Applicants arguments are not found to be persuasive because of the reasoning set forth regarding the Applicant's Declaration above.

Conclusion

Claims 34-35, 38, and 46-47 are free of the art and are allowed,

Claims 31-33, 36-37, 41-45, and 48-50 remain rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul C. Martin whose telephone number is 571-272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
Examiner
Art Unit 1657

02/16/07

Jon Weber
Supervisory Patent Examiner